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EXAMINER	
SHAFER, SHULAMITH H	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 10/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/257,650	FUJINO, MASAHIKO	
	Examiner	Art Unit	
	Shulamith H. Shafer, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,18,19,22,23,28-33 and 35-44* is/are pending in the application.

4a) Of the above claim(s) *1-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18,19,22,23,28-33 and 35-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7-26-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1647. The Examiner prosecuting this application has been changed. Any inquiries relating to the examination of the application should be directed to Shulamith H. Shafer, Art Unit 1647.

Applicant's Request for Continuing Examination, filed on 5 December 2003, and the Request for Status Information filed on 20 June 2005 have been entered in full. Claims 1-13, 18, 19, 22, 23, 28-33, 35-44 are pending in the instant application. Claims 1-13 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claim 31 has been amended to correct a claim dependency; Claims 26 and 34 have been cancelled as requested by Applicant in Response filed on 5 December 2003. Claims 18, 19, 22, 23, 28-33, and 35-44 are currently under examination.

Claim Rejections Withdrawn

The rejection of Claims 26 and 34 under 35 U.S.C. § 112, second paragraph and 35 U.S.C. § 103(a) has been withdrawn. Applicant has cancelled Claims 26 and 34, rendering the rejection of these claims under 35 U.S.C. § 112, second paragraph and 35 U.S.C. § 103(a) moot.

The provisional objection to claim 31 regarding being a substantial duplicate of claim 36 as set forth on page 2 of the previous office action (mailed 3 June 2003) is withdrawn in view of the amended claims (submitted with the RCE received in this office on the 5 December 2003).

Maintained/New Grounds of Claim Rejections

35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18, 19, 22, 23, 28-33, and 35-44 are rejected under 35 U.S.C. 112, second paragraph as being vague and indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 39, 40, 41, 42, 43, and 44, the independent claims in the instant application, recite methods using such terms as "substantially changed affinity", "similar", "substantially fails", "similar activity", "substantial reduction in activity", "normal function", "natural substances", "natural affinity" and "operate in a manner similar" without clearly defining the boundaries of what is meant by the terms, "substantial", "similar", "natural" or "normal". Neither the specification or the art have provided clear definitions of these terms.

On page 16 applicant states "The term "substantial change" as used above means a change to the extent that a disease can be caused when the affinity of the natural ligand for the normal and aberrant receptors are compared: and may be any change, whether significant or insignificant, as long as it is capable of causing a disease." A "substantial change" cannot be defined as "any change, whether significant or insignificant". On page 15, applicants discuss products which would alter functioning of "aberrant gene product": "after a substance against the aberrant gene product results in the aberrant gene product acting normally, the aberrant gene product should exhibit a response (e.g., change in intracellular concentration of responding substance in the signal transduction system of cells having the normal receptor) similar to that exhibited by the normal gene product after being operated by an operating substance

thereagainst." However, it is unclear from applicant's disclosure what the terms "similar" and "normal" refer to.

Moreover, throughout the claims, including claims 28, 29, 30, 31, 32, 33, and 35 in addition to claims listed above, the terms "operational activity", "operates", "operate in a manner similar to" are recited. These terms are not disclosed in the specification in a manner that is recognized in the art. Applicant's filing on 5 April 2001 traverses this rejection and refers to four abstracts of articles that used the quoted terms as used in the claims. However, Applicant's arguments cannot be considered persuasive, as these abstracts are not enclosed in any filing received by this Office.

Claim 44 is also rejected as being vague and indefinite for failing to include a method step reciting how one would obtain "cells expressing the gene encoding the aberrant receptor".

Claim 18, 19 and 23 are rejected as being vague and indefinite for failing to specifically disclose the gene encoding the aberrant receptor and failing to disclose from which cell the gene is isolated. Such terms as "a gene" or "a cell" can refer to any gene or any cell in any mammal.

Claim 22 is rejected as being vague and indefinite for using the term "substantially changed". How much of a change is required to be "substantial" is not clearly defined in the specification or in the art.

Claim 42 is rejected as being vague and indefinite for reciting "a substantial reduction in activity of the signal transduction system". The specification does not disclose what is meant by "substantial reduction".

Claims 36, 37 and 38 are rejected as being vague and indefinite for failing to specifically disclose whether the change in "the activity of the signal transduction system" is an increase or a decrease "in intracellular concentrations of responding substances". Concentrations of second messengers can increase or decrease in response to activation of a particular G-protein, depending on the Gα subunit.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

Claims 18, 19, 22, 23, 28-33, and 35-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant invention is drawn to a method of screening for "subject substances" which would compensate for or restore the functioning of a mutant receptor to that of a wild-type or "non-aberrant receptor". The method steps, in the broadest claims, comprise incubating mutant receptors ("aberrant receptor") with a "synthetic compound", measuring some response ("operation activity"), incubating wild-type receptors with a "natural substance", measuring some response and comparing the elicited responses

generated by the two receptors. The claims as recited further limit a "subject substance" to comprise a "synthetic compound which substantially fails to operate the non-aberrant receptor". The preamble of some recited claims (Claim 40, 41 and 42), identify the abnormal functioning of the "aberrant receptor" as causing "a disease in a mammal". The specification, which may be enabling for a method of screening for a substance that restores normal function to a known receptor with a known mutation, for example, the mutant β3 adrenergic receptor disclosed in Example 6, 7 and 8 (pages 39-41), does not reasonably provide enablement for a method of screening for a substance that restores normal function to any mutant gene product and can be used for treatment of any disease in a mammal. The specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Methods of screening for substances that affect the activity of receptors *in vitro* are old and well known in the art, and it is known that receptors with decreased binding affinity for their ligands can be activated to function at wild-type or close to wild-type levels by supplying higher levels of the cognate ligand (see for example, Birnbaumer et al., 1994; Choong et al., 1996; Kong et al., 1993; and Green et al., 1993)

However, these claims encompass any receptor having a mutation and altered activity associated with any given disease state. The specification does not disclose a single working embodiment of a specific receptor, a disease or disorder associated with a receptor having a mutation, or possible substances that would restore activity to such receptors or compensate for mutant receptor activity. Therefore the claims are not enabled.

It is well known in the art that many diseases have some genetic component leading to a predisposition for that disease. However, the exact mutation in any specific protein associated with any of these diseases has not been characterized. Applicant has listed a number of diseases and pathological states that may involve genetic predispositions but has not disclosed a single mutated receptor associated with any one of the listed disease entities. The artisan would first have to identify a specific disease state in a mammal, determine whether that disease is caused by abnormal receptor

functioning, determine whether the abnormality is due to a mutation in the structural gene for that receptor as opposed to abnormalities in the regulatory portion of the gene or in downstream signal transduction pathways, determine whether the abnormalities in receptor functioning were a result of abnormal binding to the cognate ligand, and isolate the normal and abnormal receptors before he/she could begin to utilize this method. It was well known in the art, at the time of the instant invention, that abnormal receptor functioning could be a result of mutations leading to among other things, abnormal protein folding with retention in the endoplasmic reticulum, inability of the receptor to properly insert in the cell membrane, disruptions in receptor coupling to downstream effectors or premature stop codons which abolish function by causing synthesis of truncated, unstable proteins among other abnormalities. Spiegel (1995, Ann Rev Physiol. 58:143) teaches many such defects in just a single receptor family, the G protein-coupled receptor family (See Table 1, page 149; Table 2, page 153, Table 3, page 155, and Table 4, page 158 for the many diseases caused by abnormal GPCRs and the many different mutational possibilities which can give rise to any given abnormal GPCR). The applicant does not provide any guidance as to how to determine which disease, associated with mutated receptors, could be ameliorated by a compound identified using the disclosed screening method.

Applicant does not provide any guidance to the nature or class of compounds that would be screened to detect a substance that could restore activity to an abnormal receptor but would not affect the normal, or wild-type, receptor. "Synthetic compounds" encompass a great number of structural and functional molecules. The instant specification does not disclose a single working example of a successful screening for such a compound. Applicant has not given the artisan any direction as to class of molecules, size, structural characteristics or method of synthesis. Compounds could be of any sized and synthesized *in vivo*, using cell culture techniques, or large scale manufacturing methods.

Claims 41 and 42 recite a method of screening for a drug which restores normal function to a signal transduction system. However, the specification does not disclose information about which signal transduction system would be affected by the receptor

used in the instant invention. It was well known in the art, at the time of the instant invention, that there is a great deal of cross-talk between the components of any signal transduction cascade, i.e. activation of a number of different receptors could activate the same down-stream molecule, or activation of a single receptor could activate numerous downstream effectors (see, for example, reviews by Gutkind, 1998, JBC 273:1839; van Biesen et al., 1996, Endocrine Reviews 17:698). Without specific direction and guidance, the artisan could not determine which signal transduction system would be involved in method claims 41 and 42.

Claims 40, and 42 recite screening for a substance for use in treatment of a mammal. It is well known in the art that the development of pharmaceutical therapies are unpredictable (see for example, Goodman and Gilman, 10th edition, McGraw-Hill, 2001, page 3-29) for the following reasons: (1) the identified compound may be inactivated by degradation, immunological inactivation, or inherently short half-life before producing an effect; (2) the identified compound may not reach the target area; (3) individual differences in absorption, metabolism or excretion of identified compound; (4) other functional properties may make the identified compound unsuitable for *in vivo* therapeutic use (e.g. unacceptable toxic side effects). Since the structural and functional characteristics of compounds identified by the screening methods of the instant invention are not disclosed, undue experimentation on the part of the artisan would be required to use this method of screening to identify a substance for use in treatment.

Due to the large quantity of experimentation necessary to identify a disease caused by a mutation which inhibits interaction of ligand and mutated receptor, the identification of the wild-type receptor and mutant variant, and the identification of class of compounds to be screened, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed toward the same, the complex nature of the invention, the breadth of the claims which are drawn to any receptor and any disease, the level of unpredictability in the development of pharmaceutical therapeutics, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 U.S.C. § 103(a)

The rejections of claims 18, 19, 22, 23, 28-33, and 35-44 under 35 U.S.C. § 103(a) as being unpatentable over Lebrun et al., or Birnbaumer et al., or Green et al., or Kong et al., in view of Choong et al., and further in view of Dower et al., all previously of record, is maintained for reasons of record in the previous Office Actions.

Applicant traverses the rejection and asserts on page 10 of the response filed on 5 December 2003 that the claimed invention is directed to a method of finding a synthetic substance which, when contacted with an aberrant receptor whose affinity for its natural substrate is impaired, causes the aberrant receptor to operate in a manner similar to the non-aberrant receptor. Applicant asserts that none of the references disclose that concept. Applicant states that the primary reference, Lebrun et al., does not teach mutant receptors having impaired binding for their natural substrate, does not utilize synthetic substances, and does not compare the operation of such a substance on the aberrant receptor to the operation activity of the natural substance on the non-aberrant receptor. Applicant asserts that the other primary references are even less relevant than Lebrun et al. and that the Dower et al. Patent does not remedy the defects of the other references.

Applicant's arguments filed 5 December 2003 have been fully considered but are not deemed persuasive. The requirement that the aberrant receptor have substantially changed affinity for natural substances (Claim 39, 40, 42, 43 and 44), or cause a disease by affecting the signal transduction system (Claim 41), are all stated in the preamble. The wording of these preambles, utilizing such terms as "substantially changed", "similar", "natural affinity", "normal function" which are poorly defined in the specification, do not present clear limitations of the claims and thus have not been given patentable weight. The instant invention reads on method steps for screening compounds. The references cited by the examiner, Lebrun et al., Birnbaumer et al., Green et al., Kong et al., and Choong et al., all teach *in vitro* systems for studying the

functioning of mutated receptors compared to their wild-type counterparts. Thus they all teach method steps comprising bringing an "aberrant receptor into contact with a subject substance", "determining the operation activity of said subject substance on said receptor", "bringing the non-aberrant receptor into contact with a natural substance", "determining the operation activity" of the natural substance on the non-aberrant receptor, and comparing the two "operation" activities. Therefore, the essential method steps recited in claims 39, 40, 41, 42, 43, and 44 are taught by the cited references. Lebrun et al. do not describe mutant receptors with impaired binding for natural substrate, but they do teach an "aberrant receptor which affects the signal transduction system of the cell" as recited in the preamble to Claim 41. Applicant asserts that Lebrun et al. did not utilize "synthetic substance" but used monoclonal antibodies. In the absence of clear guidance in the specification as to chemical nature, size or structure of a "synthetic compound", or the nature of the synthetic process, the term may reasonably be interpreted as any molecule synthesized by any means: *in vivo*, using cell culture techniques, or large scale manufacturing methods. Monoclonal antibodies are synthesized by hybridoma cells in cell culture systems, thereby meeting the definition of synthetic compounds. Figure 1 on page 11274 of the Lebrun paper teaches that the monoclonal antibody (anti-(458-465) does not affect insulin binding to the wild-type receptor, thereby meeting the condition of a "synthetic compound which substantially fails to operate the non-aberrant receptor".

Lebrun et al teach method steps for screening for compounds that would activate an insulin receptor with a mutation that impairs the ability of the "natural substance", the hormone insulin, to activate downstream signaling cascades and generate a physiological response; this mutation does not affect the binding of insulin to the receptor. One of ordinary skill in the art would be aware that impaired physiological responses to insulin could occur because of a wide variety of abnormalities in receptor structure caused by many different types of mutations, including mutations that would directly affect ligand-receptor binding. Therefore, one of ordinary skill in that art would have been motivated to use the screening method of Lebrun et al., with a receptor that had a mutation that affected ligand binding, since one of ordinary skill in the art would

want to screen for drugs that could be used to therapeutically treat individuals that had such a mutant receptor. The other references (Birnbaumer et al., Green et al., Kong et al., and Choong et al.) teach how common mutations in the ligand-binding domain of receptors are, and that such mutant receptors could be used to screen for compounds that would bind and activate them.

Applicant asserts that Lebrun et al. and the other cited references (Birnbaumer et al., Green et al., Kong et al., and Choong et al.) do not teach any "screening assays". Applicant's arguments filed 5 December 2003 have been fully considered but they are not deemed to be persuasive. Applicant's specification does not disclose any particular screening assay or method (e.g. high throughput screening). Screening assays could therefore be considered to encompass dose-response studies involving one compound, studies comparing two different compounds, or examining hundreds of compounds from commercial screening kits in a single assay. The claims in the instant invention recite method steps comprising: 1. contacting aberrant receptor with a subject substance; 2. determining "operation activity" of said subject substance on said receptor; 3. bringing non-aberrant receptor into contact with a natural substance; 4. determining the "operation activity" in (3); and 5. comparing "operation activity" in step (2) to that of step (4). Therefore, any study that teaches method steps comparing the functioning of a wild-type receptor with its mutant variants in response to test compounds would meet the definitions of a screening assay.

Applicant states that Lebrun et al., Birnbaumer et al., Green et al., Kong et al., and Choong et al. do not teach "screening assays" since these studies to not explicitly state that screening for compounds to overcome the deficient functioning of mutant receptors is the goal or motivation of the investigations. Applicant asserts that "every one of these references is a mechanistic study of its respective receptor. ....the authors' use of compounds to investigate the activity of the receptors was in furtherance of the goal of understanding the mechanistic action of the receptors" (Pages 12 and 14-15 in filing of 5 December 2003). Applicant's arguments have been fully considered but they are not deemed to be persuasive. The claims of the instant invention are all drawn to method steps. As discussed above, the cited references all recite method steps

comprising: 1. contacting aberrant receptor with a subject substance; 2. determining "operation activity" of said subject substance on said receptor; 3. bringing non-aberrant receptor into contact with a natural substance; 4. determining the operation activity in (3) and 5. comparing operation activity in step (2) to that of step (4). The motivation or goal of the artisan carrying out these method steps is immaterial. The method steps are the important teachings of the cited references. Comparing the functioning of a mutant receptor to its wild-type or normal counterpart following incubation with a given compound would constitute the outlines of a screening assay, even if it is not specifically taught as such.

Applicant also asserts that because the "mechanism of nuclear receptor action is .....different from that of a transmembrane receptor" one of skill in the art would have no motivation to combine the teachings of the above cited references (Page 15 in filing of 5 December 2003). Applicant's arguments have been fully considered but they are not deemed to be persuasive. The independent claims of the instant invention do not limit or identify the class of receptors to be used in the recited "screening" steps. The skilled artisan is aware that many signal transduction pathways converge in the nucleus and would be motivated to combine teachings from nuclear receptor art with those of transmembrane receptor art. A person of ordinary skill in the art would reasonably have expected success because Lebrun et al. teach that mutant receptors can respond and generate downstream signals when contacted with a monoclonal antibody (that does not impair the ability of the normal receptor to bind its cognate ligand) that changes the conformation of the receptor; Birnbaumer et al., Green et al., and Choong et al. teach that mutant receptors can respond and generate downstream signals when contacted with higher doses of the cognate ligand.

Applicant traverses the Examiner's statement that the method steps taught in the prior art are the relevant disclosures, not the results obtained using those method steps. Applicant states that "identification of a compound which causes an aberrant receptor to operate in a manner similar to the non-aberrant receptor is the *raison d'être* of the pending claims. Furthermore, Birnbaumer et al. do not disclose the use of a synthetic compound which substantially fails to operate the non-aberrant receptor" (Page 13-14 in

filing of 5 December 2003). Applicant's arguments have been fully considered but they are not deemed to be persuasive. The claims of the instant invention are all drawn to methods (see discussion above), not to a product or compound identified at the end of the process (method).

The combined teachings of the references teach exactly the method steps recited in the claims. The method steps of the claimed invention comprise first contacting aberrant receptor with a subject substance said subject substance comprising a synthetic compound which substantially fails to operate the non-aberrant receptor. Lebrun et al. teach incubating the wild-type and the mutant receptor receptors with antibodies (page 11273, column 2, paragraph 6). These antibodies were produced by hybridoma cells (page 11273, column 1 paragraph 3), meeting the claim limitation of a synthetic compound. These antibodies do not affect the ability of the wild-type receptor to bind insulin (page 11273, column 2 paragraph 6 and page 11274, figure 1), thus meeting the limitation of a "compound which substantially fails to operate the non-aberrant receptor". Lebrun et al. teach that incubating the mutant receptor with monoclonal antibodies restores its ability to activate tyrosine kinase, initiating downstream signaling cascades (page 11274, column 1, paragraph 2 over onto column 2, paragraph 1 and page 11275, Figure 4), thus determining "operation activity" (restoration of the ability of insulin binding to receptor to activate tyrosine kinase) of said subject substance (the monoclonal antibody) on said receptor, fulfilling step 2 of the method steps recited in the claims. It is well known in the art (see for example, discussion in Lebrun, et al., page 11272, column 1, paragraph 1, over into column 2) that hormone binding to the α-subunit of the insulin receptor activates the receptor kinase; thus, the "operation activity" of the "non-aberrant receptor" in response to insulin binding is well known to one of ordinary skill in the art. Lebrun et al. thus teach a method of bringing an aberrant receptor (mutated insulin receptor) into contact with a synthetic substance (monoclonal antibody) which substantially fails to operate the non-aberrant receptor (does not interfere with insulin binding to the wild-type receptor), and determining the operation activity of said subject substance (antibody) on said receptor (mutant receptor), the operation activity being activation of receptor tyrosine kinase

upon binding of insulin to the mutated receptor. Therefore, Lebrun et al. does recite components of a "screening method", i.e. bringing a mutated receptor in contact with a compound and assessing the ability of that receptor to function in a manner similar to that of the wild-type receptor. Lebrun does not teach a receptor which has "substantially changed affinity for natural substances that have a natural affinity for a non-aberrant receptor". Birnbaumer et al. teach a mutant vasopressin receptor (Q3 receptor) which has a 19.5-fold lower affinity for AVP compared to the wild-type receptor (page 887, column 2 and page 888, Figure 2), thus teaching a receptor with substantially changed affinity for natural substances. Birnbaumer et al. (page 889, Figure 3) teach an assay comprising incubating homogenates obtained from cells expressing the wild-type and mutant receptor. They compare the effects of increasing concentrations of AVP on the adenylyl cyclase activity of the homogenates. Therefore, they teach a method of bringing aberrant and normal receptors into contact with a substance (increasing concentrations of AVP) and determining and comparing the operation activity (adenylyl cyclase activity) of the two receptors. The basic steps of the method, recited by the instant invention, are thus taught by Birnbaumer et al. (see discussion above). Green et al. teach a mutant β_2-adrenergic receptor (β_2-AR) with impaired binding ability (about a 3.5-fold decrease in K_i) for its natural ligand, epinephrine (Page 23116, Abstract), thus teaching a receptor with substantially changed affinity for natural substances. The reference compares the effects of incubating membranes from cells expressing wild-type and mutant β_2-AR with various concentrations of epinephrine on stimulation of andenylyl cyclase activity. Therefore, Green et al. teach the basic method steps disclosed in the instant invention comprising bringing aberrant and normal receptors into contact with a substance (increasing concentrations of epinephrine) and determining and comparing the operation activity (adenylyl cyclase activity) of the two receptors. Kong et al. teach a mutant σ opoid receptor which has reduced affinity for σ receptor-selective agonists (Page 23055, Abstract and page 23056, Figure 1 and page 23057, Figure 3 and Table 1). The binding of radioactive ligand was reduced approximately 75% compared to the wild-type receptor (page 23056, column 1, paragraph 3) thus teaching a receptor with

substantially changed affinity for natural substances. The authors teach a "screening assay" in which COS-7 cells stably express both the wild-type and mutant receptors (page 23056, column 1, paragraph 3) are treated with a number of different opoid agonists and antagonists. Kong et al. compare inhibition of forskolin-stimulated cAMP formation in COS cells expressing the wild-type and mutant σ receptor incubated with a panel of opoid agonists (page 23056, Figure 2). Thus, this reference teaches the method steps of comparing the activity of a mutant receptor to that of a wild-type receptor when challenged with a "screening panel" of agonists and meets the limitations of the basic method steps disclosed in the claimed invention. Choong et al. teach a mutation in the ligand binding domain of the androgen receptor (AR), in which the mutant receptor was functionally impaired in terms of its ability to bind DHT, meeting the limitation of a receptor with substantially changed affinity for natural substances (page 237, column 1, paragraph 2 and page 240 Figures 3A and B) and was much less active than the normal receptor in its ability to activate transcription of an androgen-responsive reporter gene (page 237, column 1, paragraph 2 and page 241 Figure 6). This cited reference teaches the use of CV-1 cells stably expressing wild-type or mutant AR. These cells are also expressing a reporter gene (steroid response element coupled to the CAT gene), thus allowing for measurement of the "operational activity" of the receptor (page 238, column 2, last paragraph over into page 239, column 1, first paragraph). Choong et al. teach an assay comprising: (1) incubating CV-1 cells transfected with the CAT reporter gene and expressing either normal or mutant AR receptors with DHT (the ligand for the AR receptor); (2) evaluating the dose-dependent induction of CAT activity (Page 241 column 1 and Figure 6) and (3) comparing the responses of the two cell types to varying doses of DHT. Therefore, Choong et al. teaches the essential components of the method steps disclosed by the instant invention: 1. contacting aberrant receptor with a subject substance; 2. determining "operation activity" of said subject substance on said receptor; 3. bringing non-aberrant receptor into contact with a natural substance; 4. determining the operation activity in (3) and 5. comparing operation activity in step (2) to that of step (4). Thus, all the references, when combined teach exactly the method steps recited in the claims.

Furthermore, Applicant's arguments that the references have not successfully identified a compound with the required activities is not persuasive, since the instant application also does not teach the successful identification of such compounds. Applicant is improperly holding the prior art to a higher standard that their own specification.

Applicant traverses Examiner's maintenance of the rejections over the references cited above further in view of Dower et al. Applicant objects to the labeling the teachings of the above cited references as "screening assays" and states that one skilled in the art would not have been motivated to combine these references with Dower et al. Applicant's arguments have been fully considered but they are not deemed to be persuasive. As discussed above, any assay which recites method steps involving comparing the response of wild-type receptor to its mutant variant in the presence of a test compound could be interpreted as a screening assay. Thus, one of ordinary skill in the art at the time of the invention would have been motivated to use the screening methods of Dower et al., in which large numbers of chemically synthesized molecules and natural products could be screened in the receptor assays cited in Lebrun et al., Birnbaumer et al., Green et al., Kong et al., and Choong et al. to identify compounds that could activate the mutant receptor (which did not respond to the cognate ligand) in order to search for compounds in the development of new pharmaceutical agents. One of ordinary skill in the art at the time of the invention would have a reasonable expectation of success since screening combinatorial libraries for therapeutic compounds had been used extensively in the pharmaceutical industry.

Conclusions

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shulamith H. Shafer, Ph.D. whose telephone number is 571-272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, Ph.D. can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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